

The C-MIC II follow-up study: safety and efficacy results 12 months after deactivation of cardiac microcurrent therapy

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Abstract

Aims

The C-MIC II trial demonstrated benefits of 6 months of cardiac microcurrent (C-MIC) therapy in patients with nonischaemic heart failure with reduced ejection fraction (HFrEF). The prospective C-MIC II follow-up study evaluates safety and efficacy outcomes post-device deactivation.

Methods

Primary safety-related endpoints included all-cause, cardiovascular and device-related mortality, hospitalizations, and adverse events (AEs). Secondary efficacy-related endpoints included changes in left ventricular ejection fraction (LVEF), Kansas City Cardiomyopathy Questionnaire Overall Summary Score (KCCQ-OSS), 6-min walk distance (6MWD), New York Heart Association (NYHA) class, and device reactivation rate. Here, we report 12-month results comparing the 6-month time point (at the end of active therapy) with the 18-month time point (12 months post-deactivation).

Results

Of 32 eligible patients, 31 (97%) were enrolled. At 12 months post-device deactivation, 3 patients (10%) were hospitalized and 1 died (3%); none were device-related. One device-related AE occurred and was resolved completely. Improvements in LVEF [vs pre-implantation: +6%; 95% confidence interval (CI) 5–8; $P < .0001$] and KCCQ-OSS (vs pre-implantation: +43 points; 95% CI 36–49; $P < .0001$) were sustained and unchanged from 6 months (LVEF: –0.1%; 95% CI –2 to 2; $P = .87$; KCCQ-OSS: –2; 95% CI –8 to 4; $P = .49$). The 6MWD remained improved (vs pre-implantation: +150 m; 95% CI 109–191; $P < .0001$), with a modest decrease (–31 m; 95% CI –56 to –7; $P = .013$) from 6 months.

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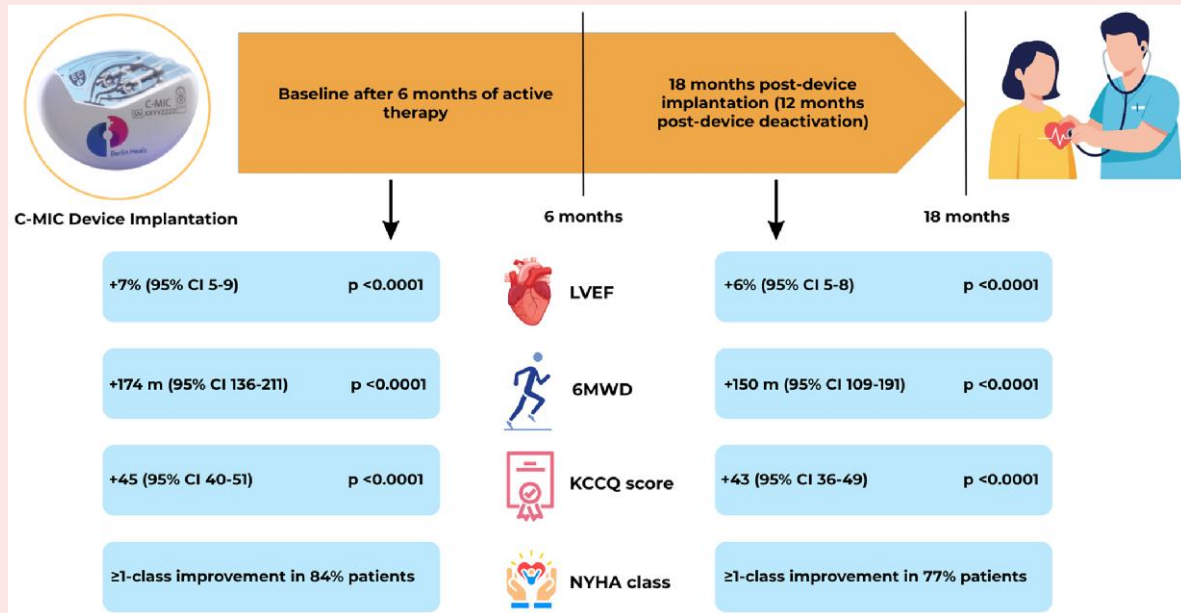
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Improvements in NYHA class (≥ 1 -class improvement in 77% patients) were sustained. Three (10%) patients required device reactivation.

Conclusion

Among patients previously treated with C-MIC device, improvements in LVEF, 6MWD, NYHA class, and KCCQ-OSS were sustained, with a favourable safety profile 12 months post-deactivation.

Graphical abstract



Outcomes of C-MIC therapy 12 months after device deactivation. C-MIC therapy is associated with sustained improvements in LVEF, functional status, and patient-reported outcomes in ambulatory patients with nonischaemic HFrEF, maintained at 12 months after device deactivation. Abbreviations: 6MWD, 6-minute walk distance; C-MIC, cardiac microcurrent; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Keywords

Cardio-microcurrent device • Electrical microcurrent • Heart failure

Introduction

Heart failure (HF) with reduced ejection fraction (HFrEF) affects an estimated 60–70 million individuals globally and is associated with substantial morbidity and mortality, often progressing despite guideline-directed medical therapy (GDMT).^{1–4} In chronic HFrEF, particularly among patients with New York Heart Association (NYHA) Class III–IV symptoms, device-based therapies may improve patient outcomes and quality of life.^{5,6}

The cardiac microcurrent (C-MIC) device is a novel, surgically implanted system that delivers non-stimulatory low-level direct microcurrents to the myocardium to promote left ventricular (LV) recovery in chronic HF.^{7–9} This approach restores an endogenous cardiomyocyte membrane potential gradient critical for proper cellular functioning, promoting reverse remodelling and facilitating tissue repair.^{9–11} In chronic cardiomyopathic failure, microcurrent therapy may also reduce myocardial oedema, thereby enhancing ventricular compliance and systolic function.^{12,13}

In an initial feasibility study of 10 patients with chronic HFrEF, C-MIC therapy was associated with improvements in LV ejection fraction (LVEF), 6-min walk distance (6MWD), and quality of life at 6 months, with sustained effects observed up to 2 years after device deactivation.^{9,14} Subsequently, the multicentre, randomized C-MIC II trial

evaluated the efficacy of the C-MIC device in 32 patients with non-ischaemic dilated cardiomyopathy (LVEF 25–35%) and NYHA class III–IV symptoms despite maximally tolerated medical therapy. C-MIC therapy resulted in a 7% absolute increase in LVEF, along with improvements in symptoms, quality of life, and a $\geq 30\%$ increase in 6MWD after 6 months of active therapy.¹⁵ However, the long-term treatment effect following device deactivation remains uncertain. The C-MIC II follow-up study aims to evaluate the safety associated with extended use, device abandonment, or system explantation, as well as clinical, functional, and echocardiographic outcomes for up to 24 months post-therapy discontinuation. Here, we report the results through 12-month post-deactivation, comparing the 6-month time point (at the end of active therapy) with the 18-month time point (i.e. 12 months after deactivating the C-MIC device).

Methods

Study design

C-MIC II (hereafter referred to as the parent trial) was a multicentre, randomized, open-label clinical trial comparing the safety and efficacy of the C-MIC system in addition to GDMT versus medication alone in patients

with chronic HFrEF (ClinicalTrials.gov Identifier: NCT04662034). Details of the study design and implantation procedure have been reported previously.¹⁵ Patients in the treatment arm who completed 6 months of active therapy and underwent device deactivation per protocol were screened for participation and enrolled in the ongoing prospective C-MIC II follow-up study, which was designed to assess the safety and durability of C-MIC therapy (ClinicalTrials.gov Identifier: NCT05189860). The study protocol was developed by the principal investigators and the sponsor (Berlin Heals) and approved by the ethics committee at each participating centre. The study complied with the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Council for Harmonization. An independent data monitoring committee evaluated patient safety. All participants provided written informed consent.

Inclusion and exclusion criteria

All patients enrolled in the C-MIC II trial who were treated with the C-MIC device for 6 months were eligible for participation in the C-MIC II follow-up study. In the parent trial, eligible patients were ambulatory adults with chronic non-ischaemic dilated cardiomyopathy of 1–5 years duration, LVEF of 25–35%, and NYHA Class III–IV symptoms despite optimal GDMT. Key exclusion criteria included ischaemic aetiology of HF, structural heart disease (including congenital or valvular disease), recent use of inotropic support within 30 days prior to enrolment, or anatomical contraindications to C-MIC device implantation. All patients from the per-protocol treatment group who provided written informed consent were included in the follow-up study and those who were unwilling or unable to attend follow-up visits were excluded.

Patient follow-up

Clinical assessments were performed at baseline (pre-implantation). Following device deactivation at 6 months, patients were evaluated at 6-month intervals for up to 24 months. Core laboratory echocardiographic assessments were performed every 6 months after deactivation. Patients who required device reactivation, defined as a decrease in LVEF of more than 5% from the 6-month value at the end of active therapy or an LVEF <35%, underwent additional evaluations at 1 and 6 months post-reactivation and at 24 months.

Trial outcomes

The primary endpoints were designed to assess the long-term safety of the C-MIC device following deactivation after 6 months of active therapy. These included rates of all-cause, cardiovascular, and device-related mortality, all-cause hospitalizations, cardiac and device-related hospitalizations, rate of device implantation [implantable cardioverter defibrillator (ICD), cardiac resynchronization therapy (CRT), and left ventricular assist device (LVAD)], heart transplantation, the composite of rate of death or cardiac-related hospitalization, or device implantation or heart transplantation, the overall incidence and severity of adverse events (AEs) and device malfunction.

The secondary endpoints evaluated the long-term efficacy of the C-MIC device and included changes in LVEF assessed by core-lab echocardiography, Kansas City Cardiomyopathy Questionnaire Overall Summary Score (KCCQ-OSS), 6-min walk distance (6MWD), the proportion of patients with ≥1 class improvement in NYHA functional class, changes in weight-adjusted peak oxygen consumption (VO₂), N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, and the rate of device reactivation to evaluate the need for prolonged therapy with the C-MIC system. Other secondary endpoints included the changes in left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV), LV mass and LV mass index, as assessed by the echocardiography core laboratory.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median with interquartile range, and categorical variables as counts and percentages. Continuous outcomes were analysed using the mixed model repeated measures approach for comparisons between multiple time points and baseline (pre-implantation), incorporating baseline values as covariates along with treatment, time, and treatment-by-time interaction as factors. Least-squares mean changes from baseline, corresponding 95%

Table 1 Pre-implantation baseline characteristics

	Patient data (N = 31)
Age (years)	58 ± 10
Women, n (%)	9 (29)
Body mass index (kg/m ²)	28 ± 5
Body surface area (m ²)	2 ± 0
Duration of heart failure (years)	2.7 ± 1.5
Left ventricular ejection fraction (%)	30 ± 4
Kansas City Cardiomyopathy Questionnaire overall score	46 ± 20
New York Heart Association class III, n (%)	25 (97)
New York Heart Association class IV, n (%)	1 (3)
Peak oxygen consumption (ml/kg/min)	17 ± 5
6-min walk distance (m)	301 ± 62
N-terminal pro-B-type natriuretic peptide (pg/ml)	1108 ± 1379
N-terminal pro-B-type natriuretic peptide (pg/ml) (log scale)	6 ± 1

Data are expressed as mean ± standard deviation, unless otherwise indicated.

confidence intervals, and nominal two-sided *P*-values were estimated at each time point. For the analysis of secondary endpoints assessing the durability of treatment effect following device deactivation, patients who required therapy reactivation were censored at the time of device reactivation. Two-sided *P*-values < .05 were considered statistically significant. All analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Of 32 eligible patients from the C-MIC II treatment arm, 31 (97%) enrolled in the follow-up study between August 2021 and November 2024. Three patients missed the 12- and 18-month follow-up visits after implantation. In one patient, therapy was not turned off at the end of the 6-month active treatment period and was therefore excluded from the secondary endpoint analysis. Additionally, three patients required therapy reactivation and were censored at the time of reactivation to assess the secondary endpoints. At baseline, all participants had symptomatic chronic HFrEF managed with GDMT. The mean age was 58 ± 10 years, and 71% were male, with a mean body mass index (BMI) of 28 ± 5 kg/m². The mean baseline LVEF was 30 ± 4%, and the majority (97%) were NYHA class III. The mean KCCQ overall summary score (KCCQ-OSS) was 46 ± 20 and the 6MWD was 301 ± 62 m. Baseline demographics of study participants are summarized in Table 1.

Primary endpoints

At 12 months after device deactivation, 12 AEs were reported in 9 patients (29%). Three patients (10%) experienced serious AEs (SAEs) requiring hospitalization. Of these, 2 events were cardiac-related (7%), including worsening heart failure and symptomatic extrasystoles. One case of acute pancreatitis was also reported. Two patients recovered, while one event (3%) resulted in mortality. All events were assessed as unrelated to the C-MIC device. One patient (3%) experienced a device-related AE (dyspnoea) and recovered without requiring hospitalization. No patients received ICD, CRT, LVAD implantation, or heart transplantation during the 18-month follow-up (Table 2).

Table 2 Safety endpoints

Endpoint	Safety analysis (N = 31) ^a	Safety analysis-censored (N = 31) ^b	Non-reactivation population (N = 28) ^c
All-cause death, n (%)	1 (3)	0 (0)	0 (0)
Cardiac-related death, n (%)	1 (3)	0 (0)	0 (0)
Device-related death, n (%)	0 (0)	0 (0)	0 (0)
All-cause hospitalizations, n (%)	3 (10)	2 (7)	2 (7)
Cardiac-related hospitalizations, n (%)	2 (7)	1 (3)	1 (4)
Device-related hospitalizations, n (%)	0 (0)	0 (0)	0 (0)
Number of patients with adverse events, n (%)	9 (29)	8 (26)	7 (25)
Device implantation (implantable cardioverter defibrillator, cardiac resynchronization therapy, left ventricular assist device)	0 (0)	0 (0)	0 (0)
Heart transplantation	0 (0)	0 (0)	0 (0)
Death or cardiac-related hospitalization, or device implantation or heart transplantation	3 (10)	1 (3)	1 (4)
Number of patients with serious adverse events, n (%) ^d	3 (10)	2 (7)	2 (7)
Number of C-MIC therapy-related adverse events, n (%) ^e	1 (3)	1 (3)	1 (4)
Patient outcome			
Recovered	9 (29)	9 (29)	7 (25)
Ongoing	7 (23)	7 (23)	7 (25)

^aAll patients previously enrolled in the C-MIC II trial and enrolled in the 2-year follow-up study. Adverse events were reported at 12 months following device deactivation.

^bAll patients in the safety analysis set who experienced adverse events after discontinuation and prior to restarting the C-MIC system were included.

^cAll patients without C-MIC reactivation during the follow-up study at 12 months post-device deactivation.

^dSymptomatic extrasystole in one patient, worsening heart failure in one patient, and acute pancreatitis in one patient.

^eDyspnoea in one patient.

Secondary endpoints

Figure 1 shows the mean LVEF with standard error at each follow-up, highlighting the temporal pattern of LVEF. At 18 months post-implantation (12 months after therapy deactivation), LVEF remained improved by an absolute +6% compared with the pre-implantation baseline (95% CI 5–8; $P < .0001$) and was unchanged compared with the end of the 6-month treatment period (−0.1%; 95% CI −2–2; $P = .87$) (Table 3).

Figure 2 depicts the mean change in KCCQ-OSS at each follow-up visit, illustrating the progressive improvement of patient-reported health status over time. The mean change from the pre-implantation baseline was 43 (95% CI 36–49; $P < .0001$) at 18 months, with no significant change from the end of the 6-month treatment period (−2; 95% CI −8–4; $P = .49$) (Table 3).

The 6MWD remained improved by +150 m (95% CI 109–191; $P < .0001$) at 18 months compared with the pre-implantation baseline; however, a modest decrease (−31 m; 95% CI −56–−7; $P = .013$) was observed between the end of the 6-month treatment period and 18 months (Figure 3 and Table 3). Improvement in NYHA class (≥ 1 -class improvement in 77% patients) was also sustained at 18 months (Table 3). The C-MIC system was reactivated in 3 patients (10%) at 400, 456, and 482 days post-initial C-MIC implantation due to a decline in LVEF. An intention-to-treat analysis including these patients without censoring at the time of reactivation was performed, and the corresponding changes in LVEF, KCCQ-OSS, and 6MWD are presented in Supplementary Table S1.

Cardiopulmonary exercise testing results showed no change in weight-adjusted peak VO_2 (0.3; 95% CI −2–3; $P = .8$) from the baseline. NT-proBNP levels initially rose within the first 4 weeks post-implantation, then steadily declined over 6 months and increased at 18 months compared to the pre-implantation baseline (400; 95% CI

−564–1365; log scale: 0.02; 95% CI −0.3–0.4; $P = .9$) (Table 3). At 18 months, the mean change from baseline in LVEDV was −9 mL (95% CI −25 to 8; $P = .3$), while the mean change in LVESV was −15 mL (95% CI −29 to −1; $P = .03$) (Figure 4). The reductions in LV mass (−26 g; 95% CI −53–0.6; $P = .05$) and LV mass index (−10 g/m²; 95% CI −23–2; $P = .10$) from baseline were also sustained at 18 months.

Sensitivity analyses restricted to participants with available follow-up data yielded similar results, suggesting that missing data did not influence the observed changes in efficacy endpoints (Supplementary Table S2). No significant changes were observed in HF medications throughout the study duration (Supplementary Table S3).

Discussion

In this 1-year follow-up of the first randomized controlled trial of cardiac microcurrent therapy for chronic HF, improvements in LVEF, NYHA functional class, exercise capacity, and patient-reported quality of life achieved during 6 months of active therapy were sustained at 1 year after device deactivation in the majority of patients, with three patients (10%) experiencing clinical deterioration requiring device reactivation. Moreover, no device-related hospitalizations or deaths were observed. Overall, the device was well tolerated and demonstrated a favourable safety profile. These findings suggest that the effects of cardiac microcurrent therapy may persist beyond the period of active treatment, supporting a potential disease-modifying mechanism rather than a purely symptomatic or device-dependent effect (Graphical Abstract).

This study represents an unusual and informative clinical scenario in which the majority of follow-up occurred after cessation of active therapy, providing a unique opportunity to assess the durability of treatment effects independent of ongoing device activity. Improvement in

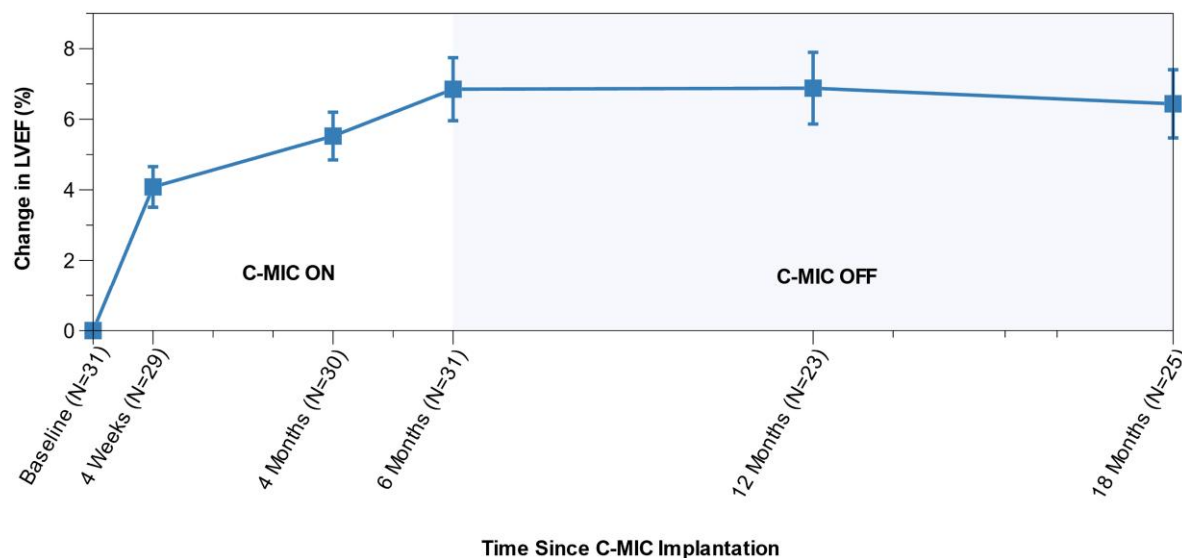


Figure 1 Change in LVEF during active treatment and following C-MIC therapy deactivation. At 18 months post-implantation (12 months after therapy deactivation), LVEF remained improved compared with the pre-implantation baseline (+6%; 95% CI 5–8; $P < .0001$) and was unchanged compared with the end of the 6-month treatment period (-0.1% ; 95% CI -2 to 2 ; $P = .87$). C-MIC, cardiac microcurrent; LVEF, left ventricular ejection fraction

LVEF is a clinically meaningful outcome in chronic dilated cardiomyopathy and is associated with improved long-term prognosis.^{16–18} C-MIC therapy has demonstrated early and sustained improvements in LVEF, with an absolute increase of 8% observed as early as 2 weeks post-implantation and maintained through 6 months in a pilot study of 10 patients.⁹ In the randomized C-MIC II trial, the mean increase in LVEF at 6 months was 7% (95% CI 5–8) in the treatment group compared with 2% in the control group. The present study focuses on the persistence of previously observed therapeutic effects after discontinuation of cardiac microcurrent therapy, highlighting the potential for sustained cardiac improvement beyond the period of active treatment. Microcurrent therapy has been shown to promote wound healing, anti-inflammatory, and regenerative effects.^{19,20} In this context, we hypothesize that the failing myocardium shares features of a chronic injury state, in which targeted electrical signalling could promote repair or recovery pathways. These observations suggest that partial ‘healing’ of the failing heart, rather than transient functional improvement alone, may be achievable. While this concept remains exploratory, the observed sustained improvements in LVEF at 18 months provide preliminary support for the possibility that myocardial dysfunction in HF may not be entirely irreversible. These results should be interpreted as hypothesis-generating, given the small sample size, lack of a control group, and the known device-related placebo effect. Although the study was not powered to assess the impact of the C-MIC device on decreasing morbidity and mortality, observational data consistently link improvements in LVEF with reduced mortality and hospitalization in HFrEF patients, supporting the need for larger, adequately powered event-driven trials to determine whether the observed improvements in cardiac function translate into meaningful reductions in clinical events.^{21–23}

Although GDMT reduces mortality in HFrEF,²⁴ many patients remain limited by poor functional status and quality of life despite maximally tolerated GDMT.^{25,26} Device-based therapies, including ICDs, LVAD, CRT, and cardiac contractility modulation, may be recommended in selected patients. Notably, ICD use was limited in our study population, and most participants had a narrow QRS duration at baseline, restricting eligibility for CRT and reflecting a distinct advanced HF

phenotype. In this context, C-MIC therapy is associated with substantial long-term improvements in symptoms, exercise capacity, and quality of life, sustained after device deactivation and exceeding those typically reported with existing device or pharmacologic therapies.^{27–29} The 6MWD, a recognized prognostic indicator in HFrEF, remained improved by 150 m at 18 months after C-MIC implantation. In contrast, a meta-analysis of 17 studies reported modest improvements with device-based interventions (CRT and cardiac contractility modulation; mean difference [MD] 20 m), baroreflex activation therapy (MD 77 m), and minimal change with medical therapy alone.²⁹

A key finding of this study is the early and preserved improvement in both patient-reported health status and functional capacity with C-MIC therapy, indicating a durable and clinically meaningful treatment effect beyond the period of active therapy. Improvements in KCCQ-OSS were observed early after treatment initiation (within 4 weeks: +29; 95% CI 23–34; $P < .001$) and were maintained at 18 months, potentially reflecting the early and preserved improvements in LVEF. Improvement in the NYHA functional class was similarly maintained in most patients. Given that enhancing quality of life and functional capacity remains a central goal in HF management,³⁰ these findings position C-MIC therapy as a promising therapeutic option for selected HF patients.

The improvements in LV volume were sustained after discontinuation of therapy and may suggest persistent biologic effects following C-MIC therapy. Sensitivity analyses restricted to participants with available follow-up data at each visit demonstrated consistent reductions in LVEDV, LVESV, and LV mass, indicating that these findings were not influenced by missing data and supporting their robustness. However, the effect of C-MIC therapy on NT-proBNP levels has been variable.^{14,15} Although patients experienced sustained improvements in symptoms, functional status, and echocardiographic measures, the mean NT-proBNP did not decline significantly during active treatment and remained unchanged at 18 months relative to 6 months. The reasons why NT-proBNP is not consistently decreased are unclear, with patient and assay heterogeneity contributing to the variability. Furthermore, the effects of microcurrent therapy on the expression, processing, or secretion of natriuretic peptides have yet to be investigated.¹⁵ Overall, given

Table 3 Efficacy endpoints

Endpoint	Baseline	6 months post-implantation	18 months post-implantation	Change from baseline to 18 months (95% confidence interval)	P-value	Change from 6 to 18 months (95% confidence interval) ^a	P-value
Left ventricular ejection fraction, (%)	30 ± 4	37 ± 6	37 ± 7	6 (5–8)	<.0001	–0.1 (–2–2)	.87
Kansas City Cardiomyopathy Questionnaire overall summary score	46 ± 20	92 ± 10	89 ± 18	43 (36–49)	<.0001	–2 (–8–4)	.49
6-min walk distance, (m)	301 ± 62	473 ± 119	451 ± 119	150 (109–191)	<.0001	–31 (–56–7)	.01
Patients with improvement in New York Heart Association class by ≥ 1 class, n (%) ^b	—	26 (84)	20 (77)	20 (77)	<.0001	—	—
N-terminal pro-B-type natriuretic peptide, (pg/ml)	1108 ± 1379	1252 ± 2555	1350 ± 2296	400 (–564–1365)	.41	–38 (–612–535)	.89
N-terminal pro-B-type natriuretic peptide ^c	6 ± 1	6 ± 1	6 ± 1	0.02 (–0.3–0.4)	.91	0.08 (–0.2–0.4)	.52
Peak oxygen consumption, (mL/min/kg)	17 ± 5	18 ± 6	17 ± 5	0.3 (–2–3)	.80	–1 (–3–1)	.33
Left ventricular end-diastolic volume, (mL)	189 ± 56	184 ± 44	184 ± 53	–9 (–25–8)	.30	–3 (–15–9)	.59
Left ventricular end-systolic volume, (mL)	132 ± 41	117 ± 36	118 ± 45	–15 (–29–1)	.03	–0.3 (–11–10)	.94
Left ventricle mass, (g)	272 ± 96	265 ± 74	254 ± 85	–26 (–53–0.6)	.05	–17 (–39–6)	.14
Left ventricle mass index, (g/m ²)	131 ± 44	129 ± 33	119 ± 39	–10 (–23–2)	.10	–8 (–19–2)	.13
Device reactivation, n (%)	—	0 (0)	3 (10)	3 (10)	—	—	—

^aValues are reported as the change from 6 months (end of active treatment) to 18 months post-implantation (12 months after device deactivation). Visits after device reactivation are excluded.

^bFollow-up data for New York Heart Association class were available for 31 patients at 6 months and 26 patients at 18 months.

^cResults are expressed as a change in the natural logarithm of N-terminal pro-B-type natriuretic peptide.

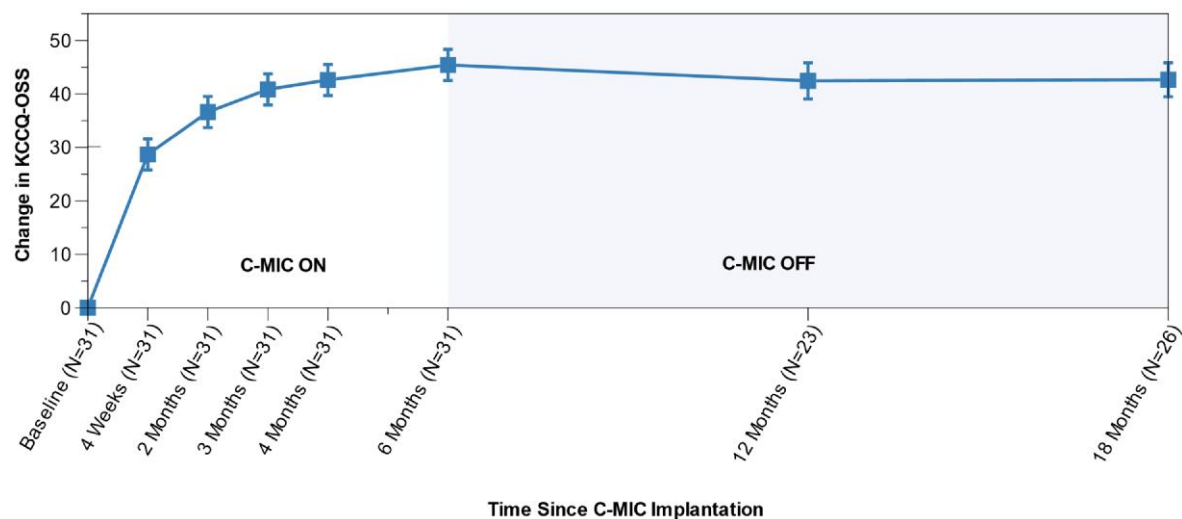


Figure 2 Change in KCCQ-OSS during active treatment and following C-MIC therapy deactivation. The improvement in KCCQ-OSS from the pre-implantation baseline was sustained at 18 months (43; 95% CI 36–49; $P < .0001$), with no significant change from the end of the 6-month treatment period (–2; 95% CI –8 to 4; $P = .49$). C-MIC, cardiac microcurrent; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire Overall Summary Score

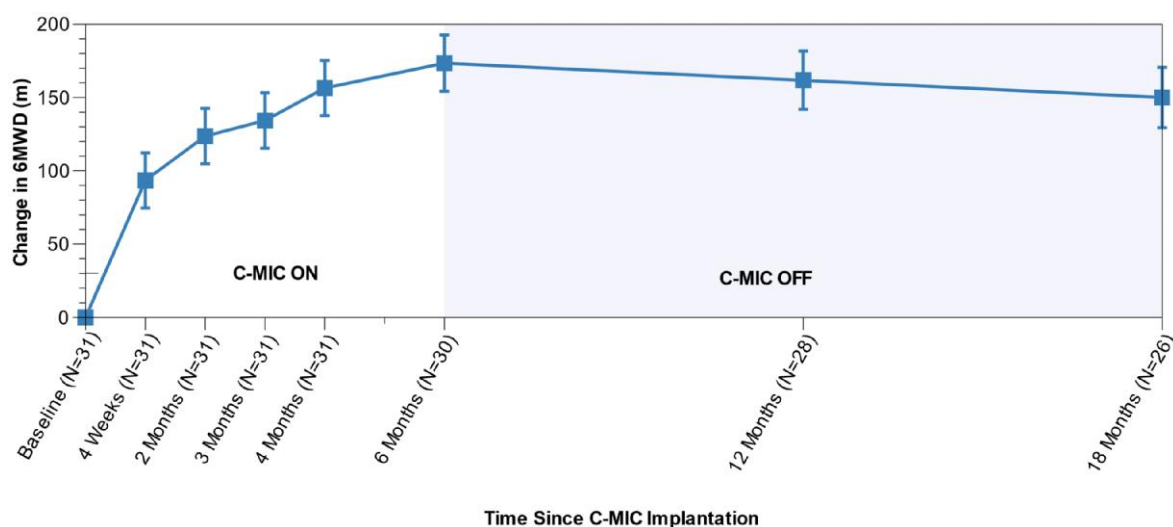


Figure 3 Change in 6MWD during active treatment and following C-MIC therapy deactivation. The 6-minute walk distance remained improved at 18 months (+150 m; 95% CI 109–191; $P < .0001$) compared with the pre-implantation baseline; however, a modest decrease (–31 m; 95% CI –56 to –7; $P = .013$) was observed between the end of the 6-month treatment period and 18 months. 6MWD, 6-minute walk distance; C-MIC, cardiac microcurrent

the small sample size and potential placebo effects, the possibility of sustained myocardial benefit remains preliminary. The impact of C-MIC therapy on NT-proBNP and structural remodelling parameters should be further evaluated in larger studies involving broader and more diverse patient populations.

The absence of a significant reduction in LV mass during active treatment, followed by a more pronounced reduction after device deactivation, may reflect a delayed structural remodelling response. C-MIC therapy may initiate biologic changes during the active treatment

period, including modulation of myocardial stress, inflammatory signalling, extracellular matrix turnover, or cellular remodelling pathways, while measurable regression in LV mass may require a longer time course to become apparent. This temporal dissociation between earlier functional improvement and later structural remodelling has been observed with other heart failure therapies and may suggest that the effects of C-MIC therapy extend beyond the active treatment period. However, given the small sample size, the lack of a concurrent long-term control group, and variability inherent to serial echocardiographic

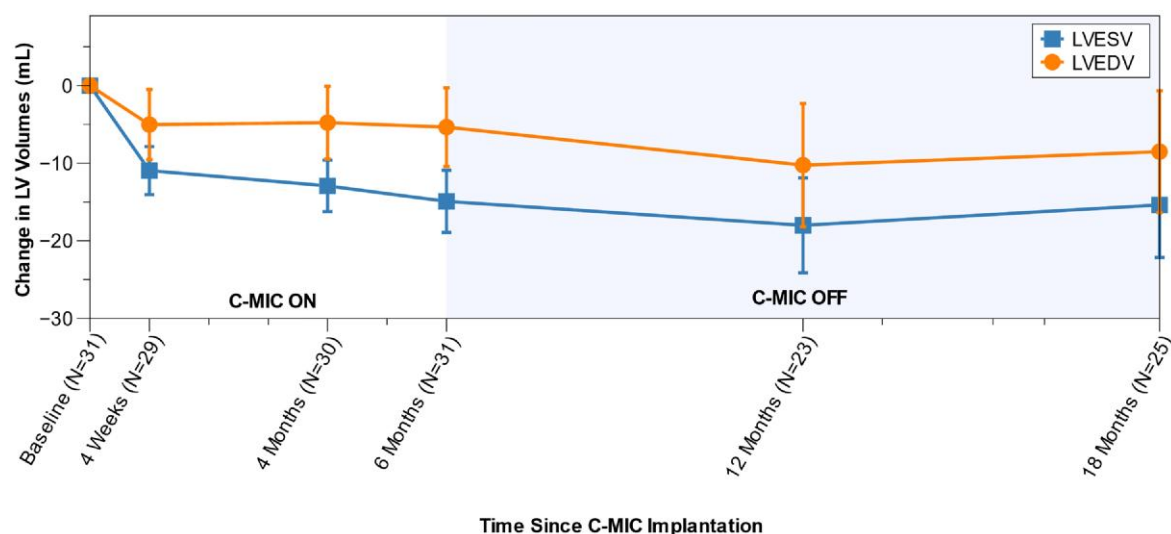


Figure 4 Change in left ventricular volumes during active treatment and following C-MIC therapy deactivation. At 18 months post-implantation, the mean change from baseline in LVEDV was -9 mL (95% CI -25 to 8 ; $P = .30$), while LVESV remained significantly reduced by -15 mL (95% CI -29 to -1 ; $P = .03$). C-MIC, cardiac microcurrent; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume.

assessment of LV mass, this hypothesis remains exploratory and should be confirmed in larger controlled studies.

At 12 months after device deactivation, one patient had died, and three were hospitalized, none of which were device-related; no deaths occurred during active therapy. Device-related AEs included dyspnoea in one patient, which resolved without hospitalization. While device deactivation is generally considered safe for inactive implantable components, three patients in this study experienced clinical deterioration necessitating reactivation, compared with only one patient in the 2-year follow-up of the pilot study.¹⁴ This suggests that deactivation may lead to symptom recurrence in some patients, underscoring the need for future studies to determine optimal therapy duration, microcurrent stimulation parameters, and patient phenotypes most likely to benefit from longer treatment.

The precise mechanism of action of C-MIC therapy remains under investigation, but preclinical studies suggest several plausible pathways.^{9–11,19,20} Future studies are needed to elucidate the mechanisms underlying these early and sustained functional improvements, determine whether prolonged therapy induces reverse remodelling, and evaluate the role of microcurrent therapy across broader HF populations, including those with ischaemic aetiologies and implanted cardiac devices. Future randomized controlled trials integrating advanced imaging, such as cardiac magnetic resonance, and biomarker endpoints will be essential to validate these mechanisms and guide patient selection for C-MIC therapy.

Limitations

This study has several limitations. First, the relatively small sample size and the absence of a concurrent control group during the post-treatment follow-up period limit the ability to definitively determine whether the sustained improvements observed after device deactivation reflect a durable treatment effect or, in part, the effects of ongoing guideline-directed medical therapy. Although biologically plausible, these findings should be considered hypothesis-generating and require confirmation in larger, controlled studies specifically designed to assess the long-term durability of the treatment effect.

Second, improvements in patient-reported outcomes, including KCCQ scores, may have been influenced by expectation and observer

bias, given the open-label nature of both the randomized phase and the long-term follow-up period following device deactivation.

Third, although the sustained improvements observed following device deactivation are encouraging, the mechanisms underlying the apparent persistence of the treatment effect remain incompletely understood. Further mechanistic studies are needed to better characterize the biological processes that may contribute to continued reverse remodelling and sustained clinical benefit after cessation of therapy.

Fourth, additional studies are needed to better characterize the subset of patients who may require prolonged or continuous active therapy to maintain clinical benefit, as well as those who may derive durable benefit after treatment discontinuation.

Fifth, participants generally had a relatively short duration of heart failure at enrolment, and all patients included in the study had non-ischaemic cardiomyopathy. Patients with earlier-stage disease may have greater myocardial plasticity and capacity for reverse remodelling, which could have contributed to the magnitude and persistence of the observed treatment effects. Therefore, these findings may not fully apply to patients with more advanced or longstanding heart failure or to patients with ischaemic cardiomyopathy, underscoring the need for further evaluation in broader and more diverse heart failure populations.

Finally, the study was conducted in Eastern Europe. Although prior evidence suggests limited regional differences in heart failure phenotypes and therapeutic response, geographic, genetic, socioeconomic, and healthcare system factors may affect generalizability. Additional studies in larger and more geographically and ethnically diverse populations are warranted to confirm the long-term sustainability of treatment effects following device deactivation.

Conclusion

In summary, C-MIC therapy is associated with sustained improvements in LVEF, exercise capacity, and patient-reported outcomes, including NYHA class and KCCQ-OSS, at 1 year after device deactivation following 6 months of active therapy. Although a subset of patients experienced clinical deterioration requiring device reactivation, these results suggest a durable therapeutic effect beyond the period of active

treatment and a potential disease-modifying mechanism with long-term myocardial functional recovery, rather than a transient physiological response. Importantly, no hospitalizations or deaths were related to the device. These findings should be interpreted as hypothesis-generating and encourage further evaluation of C-MIC therapy in larger, controlled trials.

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Supplementary data

Supplementary data are available at [European Journal of Heart Failure](#) online.

Declarations

Disclosure of Interest

Dr Rame reports receiving consulting fees from Berlin Heals and Abbott Laboratories. Dr Friede reports receiving consulting fees from Actimed, Apellis, Argenx, Bayer, Boehringer Ingelheim, Biogen, BMS, CSL Behring, Daiichi Sankyo, Galapagos, Novartis, Recardio, Relaxera, Roche, UpstreamBio, Viatrix, and Vifor. Dr Khan has received fees from Bayer. Dr Fudim reports receiving consulting fees from Berlin Heals. Dr Anker reports receiving research support from Abbott Vascular and Vifor Pharma, and personal fees from Abbott Vascular, Berlin Heals, Bayer, BRAHMS, Boehringer Ingelheim, Cardiac Dimensions, Impulse Dynamics, Novartis, Servier, and Vifor Pharma. Dr Kallel is a Berlin Heals employee.

Data Availability

The data underlying this article are not publicly available due to privacy and ethical considerations. Requests for access to study data will be considered by the sponsor on a case-by-case basis and in accordance with applicable data protection regulations.

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Ethical Approval

Ethical Approval was not required.

Pre-registered Clinical Trial Number

None supplied.

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